

# DESCRIPTION

## REMEDIES FOR SKIN ULCER

### 5 TECHNICAL FIELD

The present invention relates to a pharmaceutical composition comprising a non-prostanoid prostaglandin I<sub>2</sub> agonist as an active ingredient.

The present invention relates to a novel use of a nonprostanoid prostaglandin I<sub>2</sub> agonist.

- 10 More particularly, it is an object of the present invention to provide a pharmaceutical composition which comprises a nonprostanoid prostaglandin I<sub>2</sub> agonist as an active ingredient and is intended for use in the prevention and/or treatment of skin ulcer [e.g. diabetic skin ulcer, inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore) and the like,  
15 particularly diabetic skin ulcer, in humans or animals.

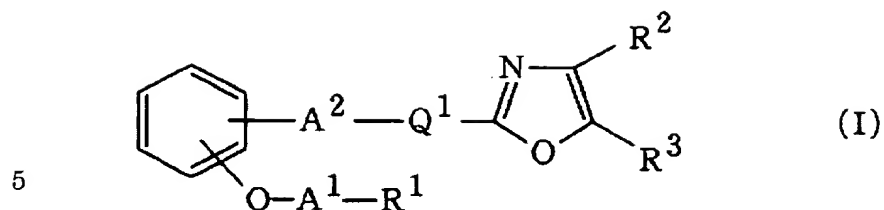
### DISCLOSURE OF INVENTION

- The inventors of this invention found that nonprostanoid prostaglandin I<sub>2</sub> agonists are useful in the prevention and/or treatment of skin ulcer [e.g. diabetic skin ulcer, inclusive  
20 of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore), particularly diabetic skin ulcer, in humans or animals and, based on this finding, they have now completed the present invention.

- The present invention is practiced by preparing a pharmaceutical composition comprising a nonprostanoid prostaglandin I<sub>2</sub> agonist as an active ingredient and administering the same to humans or animals for the prevention and/or treatment of skin ulcer [e.g.  
25 diabetic skin ulcer, inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore), particularly diabetic skin ulcer.

- The nonprostanoid prostaglandin I<sub>2</sub> agonist to be used in accordance with this invention is a prostaglandin I<sub>2</sub> agonist having no prostaglandin skeleton or  
30 bicyclo[3.3.0]octane skeleton or 2-oxabicyclo[3.3.0]octane skeleton.

Preferred as the nonprostanoid prostaglandin I<sub>2</sub> agonist in the practice of the invention are the following compounds (I):



[wherein R¹ is carboxy or protected carboxy,

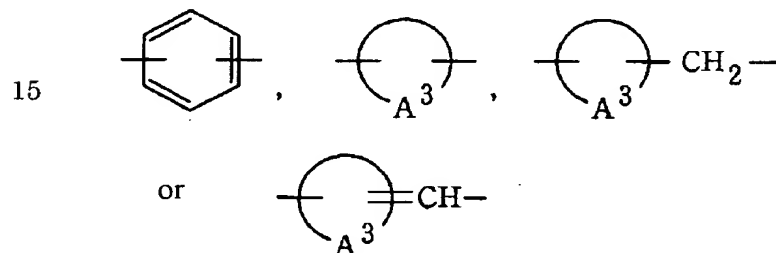
R² is aryl which may optionally have one or more suitable substituents,

R³ is aryl which may optionally have one or more suitable substituents,

10 A¹ is lower alkylene,

A² is a single bond or lower alkylene and

-Q¹- is

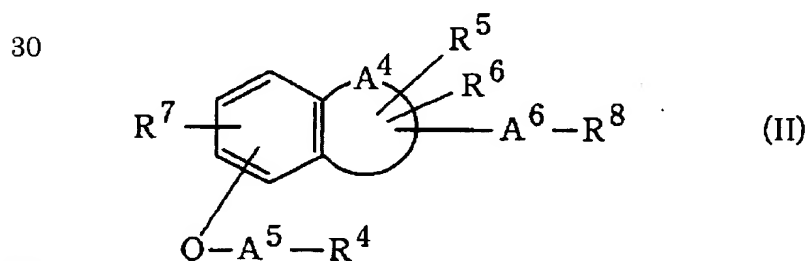


20 (in which

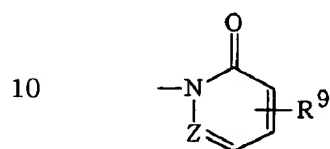


represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents]);

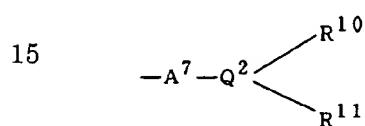
or the following compounds (II):



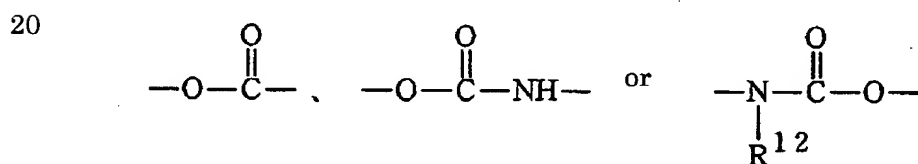
[wherein  $R^4$  is carboxy or protected carboxy,  
 $R^5$  is hydrogen, hydroxy or protected hydroxy,  
 $R^6$  is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,  
 $R^7$  is hydrogen or halogen,  
 5  $A^5$  is lower alkylene,  
 $A^6$  is a single bond or lower alkylene and  
 $-R^8$  is



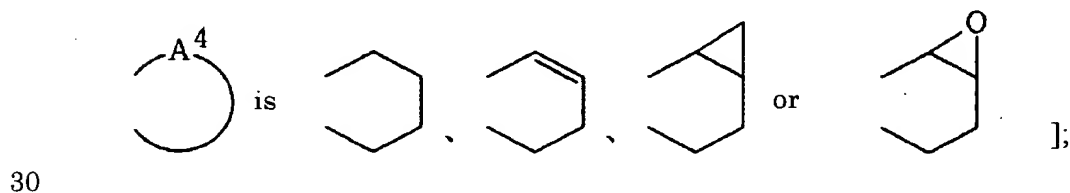
(in which  $R^9$  is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or



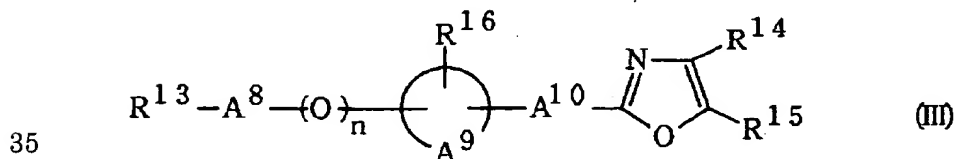
(in which  $A^7$  is



25 (in which  $R^{12}$  is hydrogen or lower alkyl),  $Q^2$  is N or CH,  $R^{10}$  is aryl and  $R^{11}$  is aryl), and

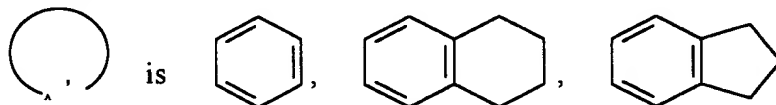


or the following compounds (III):



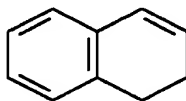
[wherein  $R^{13}$  is carboxy or protected carboxy,  
 $R^{14}$  is aryl which may optionally have one or more suitable substituents,  
 $R^{15}$  is aryl which may optionally have one or more suitable substituents,  
 $R^{16}$  is hydrogen, lower alkyl, hydroxy or aryl,

5  $A^8$  is lower alkylene,

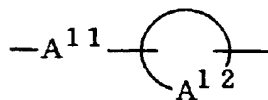


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or



$-A^{10}-$  is



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(in which  $-A^{11}-$  is a single bond,  $-\text{CH}_2-$  or  $-\text{CO}-$ ,

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represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or

25  $-X-A^{13}-$  (in which  $-X-$  is  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{N}(\text{R}^{17})-$  ( $\text{R}^{17}$  being hydrogen, lower alkyl or acyl) and  $A^{13}$  is lower alkylene which may optionally have one or more suitable substituents) and  $n$  is 0 or 1];

or pharmaceutically acceptable salts thereof.

30 Suitable salts for use as the pharmaceutically acceptable salts of compounds (I) to (III) are conventional nontoxic salts, including alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), ammonium salt, organic base salts (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt,  $\text{N,N}'$ -dibenzylethylenediamine salt, etc.), organic acid salts (e.g.  
 35 acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), inorganic acid salts (e.g. hydrochloride, hydrobromide, sulfate, phos-

phate, etc.), salts with amino acids (e.g. arginine, aspartic acid, glutamic acid, etc.) and the like.

The compounds (I) to (III) and pharmaceutically acceptable salts thereof, which are to be used in accordance with this invention, may contain one or more asymmetric centers and therefore they may exist as enantiomers or diastereoisomers. Both mixtures of such isomers and individual isomers fall within the scope of this invention.

The compounds (I) to (III) and pharmaceutically acceptable salts thereof, which are to be used in accordance with this invention, may exist a solvate and this solvate also falls within the scope of this invention. As preferred solvate, there may be mentioned hydrates, ethanolates and the like.

Radiolabeled derivatives of the compounds (I) to (III), which are suited for use in biological studies, also fall within the scope of this invention.

Referring to the above description and subsequent description in the present specification, suitable examples and specific examples falling within respective definitions given herein for defining the scope of the present invention are shown below in detail.

Unless otherwise specified, the term "lower" means that 1 to 6 carbon atoms are involved.

Suitable species of "aryl" and of "aryl moiety" of "mono(or di or tri)aryl(lower)alkyl" are phenyl, naphthyl and the like.

Preferred as "lower alkylene" are straight or branched ones containing 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene. More preferred are those containing 1 to 3 carbon atoms.

Preferred as "lower alkyl" or as "lower alkyl moiety" of "mono(or di or tri)aryl(lower)alkyl" are straight or branched ones containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl. More preferred are those containing 1 to 4 carbon atoms.

Preferred as "protected carboxy" are esterified carboxy etc.

Preferred examples of the ester moiety of the esterified carboxy are (1) lower alkyl esters (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.), which may optionally have at least one suitable substituent, thus including, for example, lower alkanoyloxy(lower)alkyl esters [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(2-, 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester,

- isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)pentanoyloxyethyl ester, etc.], lower alkylsulfonyloxy(lower)alkyl esters (e.g. 2-mesyloethyl ester etc.), mono(or di- or tri-)halo(lower)alkyl esters (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxy-carbonyloxy(lower)alkyl esters (e.g. methoxy-  
 5 carbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phthalidy-  
 lidene(lower)alkyl esters, (5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl esters [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];  
 10 (2) lower alkenyl esters (e.g. vinyl ester, allyl ester, etc.);  
 (3) lower alkynyl esters (e.g. ethynyl ester, propynyl ester, etc.);  
 (4) ar(lower)alkyl esters, which may optionally have at least one suitable substituent, for example mono(or di- or tri-)phenyl(lower)alkyl esters, which may optionally have at least one suitable substituent, (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester,  
 15 phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.);  
 (5) aryl esters which may optionally have at least one suitable substituent (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.);  
 20 (6) phthalidyl ester, and so forth.

Referring to the expression "aryl which may optionally have at least one suitable substituent", halogen, amino, hydroxy, lower alkoxy and such lower alkyl species as mentioned above are preferred as "substituent".

Suitable examples of "cyclo(lower)alkane" are cyclopropane, cyclobutane,  
 25 cyclopentane and cyclohexane.

Suitable examples of "cyclo(lower)alkene" are cyclopropene, cyclobutene, cyclopentene and cyclohexene.

Referring to the expression "cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents", epoxy, hydroxy, lower  
 30 alkoxy and the like are preferred as "substituents".

Suitable examples of "lower alkoxy" are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like.

Preferred as "protected hydroxy" are acyloxy etc.

Preferred as "acyl" and as "acyl moiety" of "acyloxy" are aliphatic acyl groups and  
 35 acyl groups having an aromatic or heterocyclic ring.

As preferred examples of the acyl, there may be mentioned lower alkanoyl groups

(e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);

lower alkoxycarbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.);

lower alkylsulfonyl groups (e.g. mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.);

arenesulfonyl groups (e.g. benzenesulfonyl, tosyl, etc.);

aroyl groups (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indanecarbonyl, etc.);

ar(lower)alkanoyl groups (e.g. phenylacetyl, phenylpropionyl, etc.);

ar(lower)alkoxycarbonyl groups (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.); and so on.

Suitable examples of "halogen" are chlorine, bromine, iodine and fluorine.

Preferred species of "cyclo(C5-C8)alkene" are cyclopentene, cyclohexene,

cyclopentene and cyclooctene.

Preferred species of "cyclo(C7-C8)alkane" are cycloheptane and cyclooctane.

Preferred as "bicycloheptane" are bicyclo[2.2.1]heptane etc.

Preferred as "bicycloheptene" are bicyclo[2.2.1]heptene such as bicyclo[2.2.1]hept-2-ene, and the like.

Referring to the expression "cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents", imino, hydroxy, oxo, such acyl species as mentioned above, imino-protecting groups and the like are preferred as "substituents".

Suitable "imino-protecting groups" are mono(or di or tri)aryl(lower)alkyl groups and the like.

Referring to the expression "lower alkylene which may optionally have one or more suitable substituents", suitable "substituents" include such lower alkyl species as mentioned above, hydroxy lower alkyl (e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl,

hydroxybutyl, hydroxypentyl, hydroxyhexyl, etc.) and the like.

Preferred embodiments of compounds (I) are as follows:

Those in which  $R^1$  is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxycarbonyl),

$R^2$  is aryl, which may optionally have one to three (more preferably one) suitable substituents (more preferably phenyl or lower alkylphenyl),

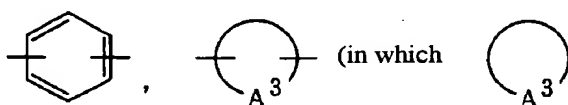
$R^3$  is aryl which may optionally have one to three (more preferably one) suitable substitu-

ents (more preferably phenyl or lower alkylphenyl),

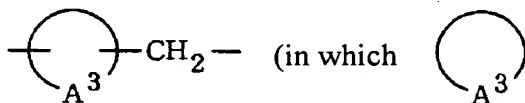
A<sup>1</sup> is lower alkylene (more preferably C1-C3 alkylene, most preferably methylene),

A<sup>2</sup> is a single bond, or lower alkylene (more preferably C1-C3 alkylene, most preferably methylene), and

5 Q<sup>1</sup>- is

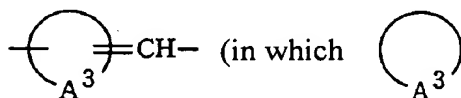


10 is cyclo(lower)alkane which may optionally have one substituent selected from the group consisting of epoxy, hydroxy and lower alkoxy, or cyclo(lower)alkene) or



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is cyclo(lower)alkane which may optionally have one substituent selected from the group consisting of epoxy and hydroxy, or cyclo(lower)alkene) or



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is cyclo(lower)alkane.

25 Preferred embodiments of compounds (II) are as follows:

Those in which R<sup>4</sup> is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxy carbonyl),

R<sup>5</sup> is hydrogen, hydroxy, or protected hydroxy (more preferably acyloxy),

R<sup>6</sup> is hydrogen, hydroxy, protected hydroxy (more preferably acyloxy), lower alkyl or halo-

30 gen,

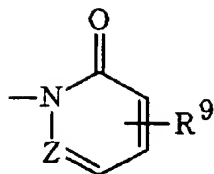
A<sup>5</sup> is lower alkylene (more preferably C1-C3 alkylene, most preferably methylene),

A<sup>6</sup> is a single bond, or lower alkylene (more preferably C1-C3 alkylene, most preferably methylene or ethylene),

-R<sup>8</sup> is

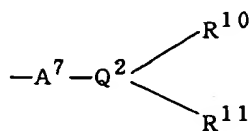
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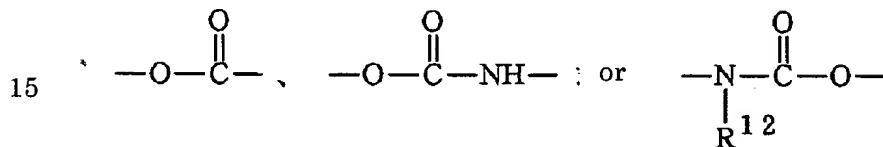
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(in which  $R^9$  is diaryl(lower)alkyl (more preferably diphenyl(lower)alkyl, most preferably diphenylmethyl) and Z is N or CH) or



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(in which  $-A^7-$  is



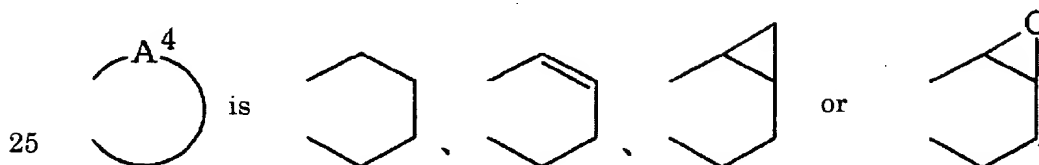
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( $R^{12}$  being hydrogen or lower alkyl),

$Q^2$  is N or CH,

20  $R^{10}$  is aryl (more preferably phenyl),

$R^{11}$  is aryl (more preferably phenyl) and



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Preferred embodiments of compounds (III) are as follows:

Those in which  $R^{13}$  is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxy carbonyl),

30  $R^{14}$  is aryl which may optionally have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl or C1-C4 alkylphenyl),

$R^{15}$  is aryl which may optionally have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl or C1-C4 alkylphenyl),

$R^{16}$  is hydrogen, lower alkyl (more preferably C1-C4 alkyl, most preferably methyl), hy-

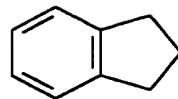
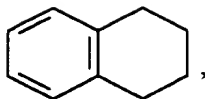
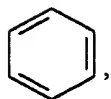
35 droxy or aryl (more preferably phenyl),

$A^8$  is lower alkylene (more preferably C1-C4 alkylene, most preferably methylene or ethyl-

ene),

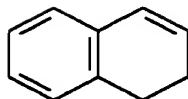


is



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or



$-A^{10}-$  is

(in which  $-A^{11}-$  is a single bond,  $-\text{CH}_2-$  or  $-\text{CO}-$ ,

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is cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane (more preferably bicy-

15 clo[2.2.1]heptane), bicycloheptene (more preferably bicyclo[2.2.1]heptene, most preferably

bicyclo[2.2.1]hept-2-ene), tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or

piperidine, which respectively may optionally have one to three (more preferably one or

20 preferably mono(di or tri)phenyl(lower)alkyl, most preferably phenyl(lower)alkyl) or

$-X-A^{13}-$  (in which  $-X-$  is  $-\text{O}-$ ,  $-\text{S}-$ , or  $-\text{N}(\text{R}^{17})-$  ( $\text{R}^{17}$  being hydrogen, lower alkyl(more pref-

erably C1-C4 alkyl) or acyl (more preferably lower alkanoyl, most preferably C1-C4

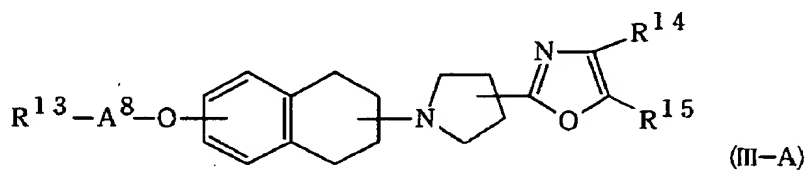
alkanoyl)) and  $A^{13}$  is lower alkylene (more preferably C1-C4 alkylene, most preferably me-

25 thylene or ethylene) which may optionally have one to three (more preferably one) suitable

substituents selected from the group consisting of lower alkyl (more preferably C1-C4 al-

ky) and hydroxy(lower)alkyl (more preferably hydroxy(C1-C4)alkyl)) and

30 (III-A):



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wherein  $\text{R}^{13}$  is carboxy, or protected carboxy (more preferably esterified carboxy, most

preferably lower alkoxycarbonyl),

R<sup>14</sup> is phenyl, or lower alkylphenyl (more preferably C1-C4 alkylphenyl),

R<sup>15</sup> is phenyl, or lower alkylphenyl (more preferably C1-C4 alkylphenyl),

A<sup>8</sup> is lower alkylene (more preferably C1-C4 alkylene, most preferably methylene).

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Particularly preferred nonprostanoid prostaglandin I<sub>2</sub> agonists to be used in the practice of the present invention are [3-[[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl]phenoxy]acetic acid, [3-[[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl]phenoxy]acetic acid,

- 10 [[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl] N,N-diphenylcarbamate,  
(1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene, [3-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]methyl]phenoxy]acetic acid and salts of these.

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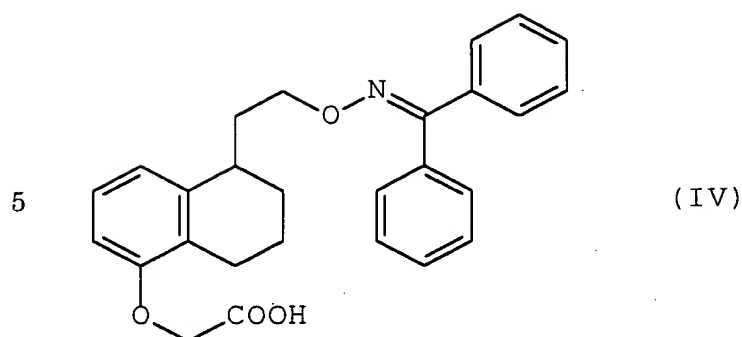
The compounds of general formulas (I), (II) and (III) as well as the specific compounds mentioned above are novel or known compounds and can be prepared by the methods described in the publications cited below or methods analogous thereto (those publications cited herein are incorporated by reference):

- 20 International publication number: WO 95/17393;  
International publication number: WO 95/24393;  
International publication number: WO 97/03973.

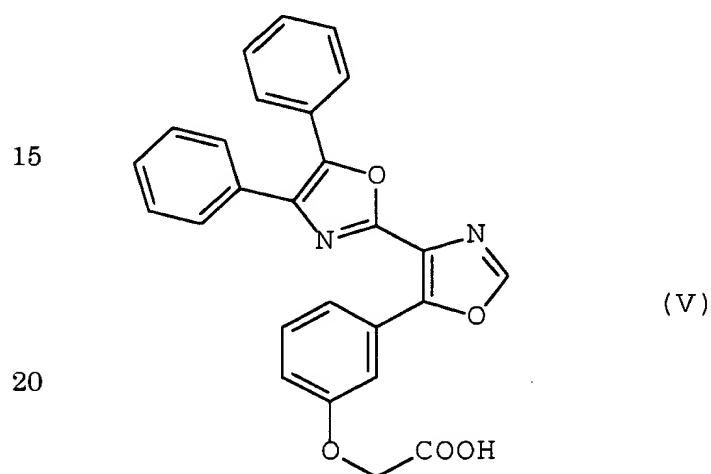
As other preferred examples of the nonprostanoid prostaglandin I<sub>2</sub> agonist which  
25 are to be used in the practice of the present invention, there may be mentioned the following:

- (1) Condensed benzene-oxyacetic acid derivatives described in European publication Nos. EP 578847 A, EP 548949 A, EP 542203 A1, EP 581187 A or EP 558062 A (those publications cited herein are incorporated by reference), preferably the compound of the following  
30 formula (IV) or salts thereof:

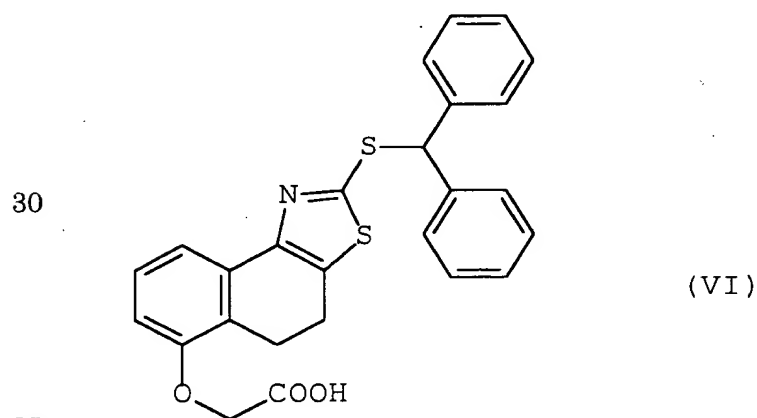
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(2) Phenoxyacetic acid derivatives described in U.S. Patent 348969 (this publication cited  
10 herein is incorporated by reference), preferably the compound of the following formula (V)  
or salts thereof:



(3) Tricyclic compounds described in International laid-open number WO 98/13356 (this  
publication cited herein is incorporated by reference), preferably the compound of the fol-  
25 lowing formula (VI) or salts thereof:



and the like.

The pharmaceutical composition for use in the prevention and/or treatment of skin ulcer according to the present invention can be used in the form of pharmaceutical preparations containing a nonprostanoid prostaglandin I<sub>2</sub> agonist as an active ingredient, for example solids, semisolids or liquids (e.g. tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders, solutions, emulsions, suspensions, etc.) suited for rectal, pulmonary (nasal or oral inhalation), transnasal, intraocular, external (local), oral or parenteral (including hypodermic, intravenous and intramuscular) routes of administration or for inhalation.

The pharmaceutical composition of this invention may contain one or more of various organic or inorganic carrier substances commonly used for pharmaceutical purposes, for example excipients (e.g. sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agents (e.g. cellulose, methylcellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose, starch, etc.), disintegrants (e.g. starch, carboxymethylcellulose, carboxymethylcellulose calcium, hydroxypropylstarch, sodium starchglycolate, sodium hydrogen carbonate, calcium phosphate, calcium citrate, etc.), lubricants (e.g. magnesium stearate, talc, sodium lauryl sulfate, etc.), flavorings or corrigents (e.g. citric acid, menthol, glycine, orange peel powder, etc.), preservatives (e.g. sodium benzoate, sodium hydrogen sulfite, methylparaben, propylparaben, etc.), stabilizers (e.g. citric acid, sodium citrate, acetic acid, etc.), suspending agents (e.g. methylcellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agents, aqueous diluents (e.g. water) and base waxes (e.g. cacao butter, polyethylene glycol, white petrolatum, etc.).

Generally, the active ingredient may be administered in a unit dose of 0.01 mg/kg to 50 mg/kg once to four times a day. However, the dosage may be increased or decreased according to the age, body weight and condition of the patient or the route of administration.

In cases where it is administered in the form of a lotion, gel or cream, the active substance may be locally administered at a concentration of 0.0001 to 10% (preferably 0.01 to 5%) several times daily, for example twice to five times daily.

#### BEST MODES FOR CARRYING OUT THE INVENTION

The test compound used as a representative example of the nonprostanoid prostaglandin I<sub>2</sub> agonist in the practice of the present invention, namely

[[[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl]

N,N-diphenylcarbamate, can be synthesized by the method described in International publication number WO 95/24393 or a method analogous thereto.

## EFFECT OF THE INVENTION

To demonstrate the usefulness of the nonprostanoid prostaglandin I<sub>2</sub> agonist used in the invention for the prevention or treatment of skin ulcer in human or animals, pharmacology test data on a representative compound, namely (1)

- 5 [[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl]  
N,N-diphenylcarbamate (hereinafter referred to as test compound), are presented below.  
Test Example 1 (db/db mouse full-thickness wound model)

### [Experimental]

- Using 10-week-old male C57BL/KsJ db/db mice (db/db mice) and the correspond-  
10 ing control C57BL/KsJ +m/+m mice (+m/+m mice), the back hair coat was removed with a  
depilatory cream. After 3 days, using ophthalmological scissors, the skin in a circular area  
with a diameter of about 1.5 cm at the dorsal midline was removed to construct a  
full-thickness wound. Thereafter, the full-thickness wound area was covered with a poly-  
urethane film agent. During 18 consecutive days beginning the day of wound construction,  
15 100 µl of the investigational compound solution or distilled water (vehicle) was taken in a  
syringe and applied through the polyurethane film once daily. The polyurethane film agent  
was changed every day and after disinfection with 3% H<sub>2</sub>O<sub>2</sub>, the drug was applied in the  
same manner as above. The wound area was measured by the tracing method under light  
anesthesia every other day as a rule. With the initial wound area at the beginning of drug  
20 application being taken as 100%, the fractional area at each day of measurement was calcu-  
lated.

### [Results]

- The wound area in db/db mice expanded slightly in an early stage following con-  
struction of the wound and thereafter diminished day by day. Compared with the wound  
25 area in +m/+m mice, the area was significantly larger at every measurement day, indicating  
a delay in healing. In contrast, in the groups treated with 0.01% and 0.1% solutions of the  
investigational drug, the early expansion of wound area was not observed and the wound  
area diminished day by day and a significant difference (p<0.05) from the vehicle control  
group was observed in wound area on and after day 7 and day 4, respectively, following  
30 construction of the wound. Comparison in the wound area on the last observation day (day  
18 following wound construction) showed that whereas the area reduction in the vehicle  
treatment group was 73%, the reductions in the groups treated with 0.01% and 0.1% solu-  
tions of the investigational compound were 90% and 93%, respectively. These results  
indicate that the investigational compound has a wound healing-promoting action.

## 35 INDUSTRIAL APPLICABILITY

The above-described nonprostanoid prostaglandin I<sub>2</sub> agonist of the invention is of

value in the prevention and/or treatment of skin ulcers (for example, diabetic skin ulcer inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.) and decubitus ulcer (bedsore), particularly diabetic skin ulcer, in humans or animals.

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